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RESEARCH ARTICLE

Randomized interventional clinical trial to estimate the efficacy of clomiphene citrate versus letrozole in induction of ovulation in infertility

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ABSTRACT

Background and objectives: Anovulation accounts for 30-40% of female infertility. The treatment of choice is by ovulation induction. This study is to estimate effectiveness of clomiphene citrate versus letrozole in ovulation induction. **Method**: 60 women with anovulatory infertility were randomised for treatment with either letrozole or clomiphene citrate for ovulation induction. After a trigger of HCG and coital advice they were observed for ovulation and pregnancy. **Results**: Ovulation rate was 80% with clomiphene citrate and 93.3% with letrozole. First cycle conception rates with letrozole was higher (23.3%) compared to clomiphene citrate (6.7%). Cumulative conception rate was 25% with clomiphene citrate and 32.1% with letrozole. Pregnancy continuation and miscarriage rates were comparable in both groups. **Conclusions**: Letrozole is better ovulating agent in infertility compared to clomiphene citrate in terms of monofolliculation and higher endometrial thickness giving good nidation rates than clomiphene citrate. Ovulation rates are comparable with both letrozole and clomiphene citrate but, first cycle conception rates are significantly better with letrozole and even cumulative pregnancy rates were higher with letrozole.

Keywords: Clomiphene citrate, letrozole, ovulation induction.

The incidence of infertility in general population is around 2.65%.[1] Ovulation induction or controlled ovarian stimulation is generally considered as the 1st line of treatment in unexplained infertility because anovulatory infertility accounts for 30-40% of female infertility[1].

The traditional ovulation induction agent is clomiphene citrate, which acts by binding to estrogen receptors in the hypothalamus blocking the negative feedback regulation over hypothalamus by oestrogen, resulting in increased secretion of gonadotrophins and subsequent ovulation. Various adverse effects like hot flushes, premenstrual symptoms, suboptimal endometrial thickness, and reduced cervical mucus secretion are noted due to antioestrogenic action of clomiphene citrate, resulting in reduced pregnancy rates due to antioestrogenic effect on endometrium, multiple pregnancy due to persistent block in negative feedback action by oestrogen on hypothalamus and recruitment of multiple cohort of follicles and hence multifolliculation and ovarian hyperstimulation syndrome. Because of which ovulation induction rate is around 60 to 75% but the conception rate is only about 20%. Therefore more effective and safe ovulatory agent is needed.

Letrozole acts by decreased aromatization of androgens resulting in reduced oestrogen which eventually promote the growth of ovarian follicles by increasing the secretion of FSH and avoiding the anti-oestrogenic effects. As the production of oestrogen increases in the cycle, intact negative feedback control by oestrogen over hypothalamus decreases release of gonadotrophins and hence selection of dominant follicle and monofolliculation. Ovulation rates of

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around 65 to 67.5% and pregnancy rates of 21% and more are seen with letrozole.

Objectives of the study: To estimate the effects of clomiphene citrate and letrozole with respect to primary objective ovulation and secondary objectives eg. endometrial thickness, number and size of follicles, pregnancy and pregnancy continuation rates.

Materials and methods

The present study was carried out in department of OBG, KIMS, Hubli Karnataka. During the period of one and half year from January 2018 to June 2019. The women were counseled and informed consent was taken and randomized into two groups by simple random method.

Inclusion criteria: All women who presented with infertility as per WHO definition of infertility (A disease of reproductive system defined by failure to achieve clinical pregnancy after 12 months or more of regular and unprotected sexual intercourse) was followed.

Exclusion criterias**:** Women who showed abnormalities in transvaginal sonography and semen analysis; those who have already undergone ovulation induction with similar drugs previously.

The study design was 'randomized interventional clinical trial.' Randomization was done by simple random method by picking chits containing codes A and B with 30 of each codes. Blinding was not followed at any stage. Women in group A received ovulation induction with clomiphene citrate and those in group B received induction with letrozole. Clomiphene citrate was given by escalating doses of 50/100/150 mg and that of letrozole in escalating doses of 2.5/5mg. In both the groups treatment was administered from day 3 to day 7 of spontaneous and withdrawal bleeding. Follicular monitoring was performed in each cycle in both the groups from day10 onwards until mature follicular diameter 18 to 22mm and trilaminar endometrial pattern was seen by TVS. Number of follicles with size and endometrial thickness in each cycle in both the groups was documented. Ovulation trigger with HCG 5000 IU intramuscularly was given to all women when a dominant follicle reached 18 mm. Ovulation was confirmed by seeing collapsed dominant follicle and free fluid in pouch of Douglas on subsequent USG. Each woman was told to have timed intercourse 24 to 48 hrs after ovulatory trigger by HCG. Women in both groups without the evidence of ovulation were asked to follow the treatment in subsequent cycles with escalating doses of clomiphene citrate/letrozole for total of 3 cycles.

Women in both groups with evidence of ovulation and negative pregnancy tests were asked to follow the treatment as a part of infertility treatment for 3 cycles with the same drug and dosage which was used in the earlier cycle. USG in all the women was performed by the same observer to eliminate the inter observer variation.

Statistical analysis: Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Independent t test or Mann Whitney u test was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively. P value (probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Results

There was no significant difference in mean age, married life, infertility and BMI between two groups (table 1). There was no significant difference in menstrual cycle, hirsutism, alopecia, amenorrhoea, acne, acanthosis, voice change and hypertension between two groups.

Table 1: Profile of subjects in two groups

Variables	Group A		Group B		P value
	Mean	SD	Mean	SD	
Age (yrs)	26.00	3.99	26.43	3.89	0.672
Married life(yrs)	5.63	3.02	6.08	4.01	0.626
Infertility(yrs)	5.00	2.73	4.82	3.01	0.806

Rates of monofolliculation was more in group B compared to group A (table 2). Size of follicle was higher in group B compared to group A in all the cycles. There was no significant difference in size of follicle between two groups in 3rd cycle (table 3).

Table 2: Mono follicular and multi follicular rate comparison between two groups

Categories		Group A		Group B	
		Count	%	Count	%
1st cycle	Monofollicular	11	36.7%	20	66.7%
	Multi follicular	17	56.7%	9	30.0%
2nd cycle	Monofollicular	14	50.0%	16	69.6%
	Multi follicular	13	46.4%	6	26.1%
Third cycle	Monofollicular	11	44.0%	15	68.2%
	Multi follicular	12	48.0%	5	22.7%

The main outcome ovulation was 80% in group A, and 93.3% in group B. There was no significant difference in ovulation rate between two groups (table 4).

Another main outcome was pregnancy which reflects the ovulation. In the study, there was no significant difference in conception rate between two groups on first cycle, second cycle, and third cycle and over all conception rate (table 5).

Table 3: Follicle size on day 16 comparison between two groups

Day 16 follicle size	Group A (mm)	Group B (mm)	P value
1st Cycle	19 x 22	21x 24	0.011*
2nd Cycle	19 x 22	21 x 24	0.004*
3rd Cycle	18 x 22	20 x 23	0.084

Table 4: Ovulation rate between two groups at respective cycle and cumulative rate

Ovulation Rate	Group A		Group B		P value
	Count	%	Count	%	
1st cycle	16	53.3%	19	63.3%	0.432
2nd cycle	18	64.3%	17	73.9%	0.461
3rd cycle	16	64%	16	72.7%	0.522
Over all	24	80%	28	93.3%	0.129

In the study 15 subjects conceived (table-6). Of them in group A, pregnancy continued in 66.7% and in group B, pregnancy continued in 88.9%. There was no significant difference in continuation between two groups. In group A, 66.7% had singleton and 33.3% had blighted ovum. In group B, 77.8% had singleton pregnancy, 11.1% had missed abortion and no follow up. There was no significant difference in outcome between two groups. There were no adverse effects in both groups.

Table 5: Pregnancy rate between two groups at respective cycle and cumulative rate

Conception rates	Group A		Group B		P value
	Count	%	Count	%	
1st cycle	2	12.5%	7	36.8%	0.101
2nd cycle	3	16.7%	1	5.9%	0.316
3rd cycle	1	6.2%	1	6.2%	1.000
Overall	6	25.0%	9	32.1%	0.571

Discussion

Both the groups are comparable with respect to married life, type and duration of infertility, hyperandrogenic features like hirsutism, acne, acanthosis and voice changes. Mean endometrial thickness (ET) on the day of starting follicular monitoring was same among both groups in first cycle and there was no statistically significant difference between the endometrial thickness on day of administering HCG. Endometrial thickness was higher in letrozole group (7.99mm) compared to clomiphene citrate (7.43mm). In 2nd cycle there was significant difference of endometrial thickness between 2 groups. Letrozole group had higher ET (8.27mm) than clomiphene citrate (7.62mm). In third cycle letrozole group had higher ET (8.54mm) than clomiphene citrate (7.57mm). The studies by KK Roy et al[6], SF Hendawy et al [7] and Shabana et al[8] showed similar results. This significant difference can be attributed to poor ET by clomiphene citrate due to anti-oestrogenic effects on endometrium.

Mean number of follicles among the two groups showed no significant difference. On comparison in first cycle

Table 6: Overall pregnancy rate comparison between two groups

Categories		Group			
		Group A		Group B	
		Count	%	Count	%
Pregnancy rate	Pregnancy negative	18	75.0%	19	70.0%
	Pregnancy positive	6	25.0%	9	30.0%
	Total	24		28	

X 2 = 0.800, DF = 1, P =0.571

multifolliculation was observed more with clomiphene citrate. With clomiphene citrate mean number of follicle on day 16 was 1.756± 0.89 and with letrozole mean number of follicle on day 16 was 1.239± 0.39.

There was significant difference in monofolliculation at day 16 between two groups. It was higher with Letrozole. The monofolliculation with letrozole was 68.2% in our study while similar results were seen with Sujata et al[9] (79.49%) and Iram Mobusher et al[10] (78.32%) which were significantly higher compared to clomiphene citrate which was 44% in our study and 54.94% in Sujata et al and 55.76% in Iram Mobusher et al.

In a study by Rokshana Ivy et al[6] the follicular growth was significantly more with letrozole (19.33mm) compared to clomiphene citrate (16.67mm). Mary Angel et al[7] observed follicular diameter similar in both groups 20.67mm vs 20.76mm with clomiphene citrate and letrozole respectively. Present study observed better follicular growth with letrozole compared to clomiphene citrate of 21×24mm vs 19×22mm in 1st cycle and 21×24mm vs 19×22mm in 2nd cycle respectively, which was found to be statistically significant. In third cycle comparable follicular growth was observed between the groups.

In present study ovulation rate with clomiphene citrate was 80% and that with letrozole was 93.3%. However there was no significant difference in ovulation rate between two groups. Amitoj Athwal et al[11], R Chakravorty et al[12] concluded that letrozole has better ovulatory rates than clomiphene citrate. Sujata Kar et al[9], KK Roy et al[6], and present study showed letrozole and clomiphene citrate had comparable ovulation rates.

In clomiphene citrate group, 12.5% and in letrozole group, 36.85% were positive for pregnancy in first cycle. Higher pregnancy rates were noted in letrozole group compared to clomiphene citrate in first cycle. Over all cumulative pregnancy rates among all cycles with Clomiphene citrate was 25% and with letrozole 32.1%. Even though letrozole group had good pregnancy rates than clomiphene citrate it was not statistically significant because of smaller sample size. The conception results observed by Sujata Kar[9], (7.84% vs 21.56%), Iram Mobusher[10] (7.42% vs

20.55%), Rekz[13] (9.8% vs36%), SA Amer [14] (43% vs 61%) were significantly higher in favour of letrozole.

In our study 15 women conceived. In them, pregnancy continued in 66.7% in clomiphene group and 88.9% in letrozole group. There was no significant difference in continuation between two groups.

In clomiphene group, 66.7% had singleton and 33.3% had blighted ovum. Four women had live births in whom 3 women were delivered by caesarean section at term and one delivered vaginally at 33weeks which needed NICU care for 2 weeks due to preterm birth with respiratory distress. In letrozole group, 77.8% had singleton pregnancy delivered at term by elective caesarean in 3 cases and vaginal delivery in 4 cases, one had missed abortion and one case could not be followed up. There was no significant difference in outcome between two groups. There were no adverse effects in both groups.

Conclusion

Letrozole is better ovulation agent in infertility compared to clomiphene citrate in terms of monofolliculation, higher endometrial thickness and ovulation rates.

Conflict of interest: None. **Disclaimer:** Nil.

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